Frailty and Cardiac Rehabilitation: a call to action from the EACPR Cardiac Rehabilitation Nucleus

Carlo Vigorito[1], Ana Abreu[2], Marco Ambrosetti[3], Romualdo Belardinelli[4], Ugo Corrà[5], Margaret Cupples[6], Constantinos H. Davos[7], Stefan Hoefer[8], Marie-Christine Iliou[9], Jean-Paul Schmid[10], Heinz Voeller[11], Patrick Doherty[12]

[1]Department of Translational Medical Sciences, University of Naples Federico II, Naples, Italy

[2]Cardiology Department Hospital Santa Marta, Centro Hospitalar Lisboa Central, Lisbon, Portugal

[3]Cardiovascular Rehabilitation Unit, Le Terrazze Clinic, Cunardo, Italy

[4]Cardiologia Riabilitativa Lancisi - AOR Ancona, Italy

[5]Department of Cardiac Rehabilitation, Salvatore Maugeri Foundation, IRCCS, Veruno (NO), Italy

[6]Department of General Practice, UKCRC Centre of Excellence for Public Health Research (NI), Queen's University, Belfast, Northern Ireland

7 Cardiovascular Research Laboratory, Biomedical Research Foundation Academy, Greece

8 Medical University Innsbruck, Austria

[9]Cardiac Rehabilitation Department, Hopital Corentin Celton-Assistance Publique Hôpitaux de Paris, France

[10]Cardiology Clinic, Tiefenau Hospital and University of Bern, Switzerland

[11]Center of Rehabilitation Research, University of Potsdam, Germany; Klinik am See, Rehabilitation Center for Internal Medicine, Rüdersdorf, Germany.

[12]Department of Health Sciences, University of York, UK

Abstract:

Frailty is a geriatric syndrome characterized by a of vulnerability status associated with declining function of multiple physiologic systems and loss of physiologic reserves. Two main models of frailty have been advanced: phenotypic model (primary frailty) or deficits accumulation model (secondary frailty), and different instruments have been proposed and validated to measure frailty. However measured, frailty correlates to medical outcomes in the elderly, and has been shown to have prognostic value for patients in different clinical settings, such as in patients with coronary artery disease, after cardiac surgery or TAVR, in patients with CHF or after LVAD implantation.

The prevalence, clinical and prognostic relevance of frailty in a Cardiac Rehabilitation (CR) setting has not yet been well characterized, despite the increasing frequency of elderly patients in CR, where frailty is likely to influence the onset, type and intensity of the exercise training program, therefore leading to design tailored rehabilitative interventions for these patients.

Therefore, we need to start looking for frailty in patients entering CR programs and become more familial with some of the most adopted tools to recognize and evaluate the severity of this condition. Furthermore, we need to better understand whether exercise-based CR may change the course and the prognosis of frailty in cardiovascular patients.

Keywords: Frailty, Cardiac Rehabilitation, Elderly

Total word count: 7446

Abstract word count: 207

Introduction

We belong to an aging world where people are living longer. In 2030, progressive population ageing will lead to an increase in the proportion of people aged over 65 from 17.4 % to 25.6 %, and the population of elderly people will almost double from 87.5 million in 2010 to 152.6 million in 2060. .[1] Progressive aging is associated with geriatric syndromes (particularly frailty) that pose a severe burden on health systems. Therefore, there is a need to better understand these syndromes, with particular attention to the relevance of frailty in the context of care of older cardiac patients, including Cardiac Rehabilitation (CR).

Frailty and its relationship with disability and comorbidity

Frailty is characterized by impairment in many domains (e.g. physical, psychological and social) with consequent effects on mortality, hospitalization, dependence, disability and significant healthcare cost.[2] Although varying definitions exist, there is a common thread in that frailty is a dynamic age-related vulnerability[3] characterized by declining function, associated with a loss of physiologic reserves of multiple organs or systems, and an increased risk of negative outcomes, such as institutionalization and death.[4,5] The pathophysiologic mechanisms underlying the development or progress of a frailty status are multifactorial, and include inflammatory mechanisms, the hypothalamic-hypophysary axis, and anabolic-catabolic hormone imbalance.[5] Studies show that frailty, independently of how it is measured, is significantly and independently correlated to medical outcomes.[6,7] Despite the relevance of frailty as a prognostic indicator, uncertainty remains regarding its definition, its measurement, the feasibility of its measurement in clinical practice and whether such measurements can be influenced by interventions or describe the progress or deterioration of health status . This is particularly true in the CR setting, where the increasing age of patients admitted to CR poses problems in individualizing models of clinical evaluation and interventions.

The extent of frailty is not determined purely by the magnitude and frequency of comorbidity or disability, since patients with the same comorbidity or disability may present with different degrees of frailty or no frailty at all. On the other hand, a patient may be frail with few comorbidities or disabilities.[8] Based on data from the Cardiovascular Health Study, about 25% of older patients show signs of frailty without either multiple comorbidities or disabilities.[9] Disability may be a consequence of frailty but, alternatively, disability may be closely linked to the development or worsening of frailty status; in particular, so called primary frailty, described in older patients without overt pathologic conditions, can lead to diseases or disability and to secondary frailty that in turn may worsen the phenotypic presentation of frailty.[10] The recognition and measurement of frailty and the possibility of modifying this status are important issues within and beyond modern geriatric medicine.

Frailty Models

Two main models of frailty have been proposed. The phenotype model proposed by Fried et al. views frailty as a biological syndrome resulting from cumulative decline across multiple physiological systems.[4] The model advanced by Rockwood et al. views frailty as a multidimensional risk state that can be measured more by the quantity than by the nature of health problems.[11-13]

Primary frailty model-The Phenotype model. According to Fried et al., a wealth of epidemiologic or observational studies have described the presence of frailty in the general elderly population (Physiologic aging). In this environment frailty has been defined as "Primary Frailty", a phenotypic presentation involving decline in physical functioning and psychological status, without taking into consideration associated diseases or pathologic conditions. Fried's Phenotype Frailty index[4] (PFI) has been widely adopted: it was derived from an analysis of five health domains: nutrition, physical exhaustion, low energy expenditure (or inactivity status), mobility, and muscular strength (Table 1). Deterioration of each of these domains was scored as 1 if present or 0 if absent, giving a potential score spanning from 0 to 5. The phenotype model classified three categories: Robust (no deterioration), pre-frail (1 or 2 function deterioration), or frail (3 or more function deterioration). This categorization was independently correlated with outcomes, such as survival, falls, disability and institutionalization.[4]

Secondary Frailty model-Accumulation of deficit model. The conceptualization of frailty proposed by Rockwood et al. considers the accumulation of multiple deficits such as symptoms, signs, disabilities, pathologic conditions, and abnormal laboratory values (Secondary Frailty).[11-14] In this model, a frailty index (FI) was measured as deficit accumulation (Table 2). Each deficit can be coded as binary (1 or 0) or ordinal (0, 0.5, 1). This FI is the sum of the deficit values divided by the total number of deficits listed (e.g. 10 deficits present out of 40 gives a FI ratio of 10/40 = 0.25) and is significantly correlated with outcomes: for example, with each unit increase the hazard rate for mortality increased by 4%.[15]

Frailty indices adopting the deficit accumulation model can be derived from different numbers and types of variables, provided certain criteria are fulfilled.[14] The number of deficits, rather than a single deficit, is related to adverse outcomes, since the final number reflects a global measure of vulnerability. A patient with a score <0.2 would be considered not frail, an increasing score indicates an increased level of frailty. In order for a FI to be able to capture sufficient features or risk factors for frailty, it should include at least 40 items, covering several health domains, such as physical, cognitive, psychological and social.[14] It is important to note that 1) frailty increase parallels aging, independently of baseline frailty, and 2) evaluation of interventions to reduce frailty must take into consideration a natural physiological increase in frailty with age.

Frailty Assessment

Assessing Instruments. An important issue in the clinical environment, and particularly in primary care, is that the measurement of frailty based on either the Phenotypic or Deficit accumulation model may be complex and time consuming. There are, however, alternative instruments to apply in clinical practice for screening and evaluating frailty in the general population (Table 3). Some follow the phenotypic model,[16-19] others consist of administered or self-administered questionnaires,[20,21] and some require clinical evaluation[22] or task performance and measurement such as the Edmonton Frailty Scale (EFS).[23] Some scales are designed to be screening instruments [18] and others to be more multifaceted tools requiring Comprehensive Geriatric Assessment (CGA).[24] They are designed for use with different groups of individuals, and differ in their feasibility and prognostic ability.

Despite these differences, all scales were predictive of all-cause mortality or of relevant elderly outcomes, in most cases independently from other prognostic indices. A recent comparison of these scales in the SHARE survey[25] showed some differences in their prognostic predictive ability. ROC curves showed that FI derived from the deficit accumulation model, FI derived from CGA (FI-CGA) and EFS performed slightly better than other scales.

Since CGA, consisting in a multidimensional assessment of several health domains, is the cornerstone of modern geriatric care,[26] FI-CGA may be considered as one of the best models to measure frailty. The FI-CGA, validated in the Canadian Study of Health and Aging (CSHA), a large

population-based study,[24-27] explored ten domains, assigning a score to each domain and constructing a frailty categorization: mild (FI-GCA 0–7), moderate (FI-CGA 7–13), severe frailty (FI-CGA >13).[24] The same data from CGA can be analyzed by counting the deficit according to the deficit accumulation model,[3] and both type of measurements have been correlated to outcome.[27]
Extensive literature has shown that frailty can indeed be measured with relative ease even in hospital settings, for patients in general medical wards,[6,7,28-31] geriatric units,[32,33] survivors of ICU or Emergency department[34,35] including critical oncologic[36] or dialyzed patients[37] (Table 4). In these settings, frailty has been assessed by a variety of tools including the FI-CGA instrument,[28,30] the CSHA Clinical Frailty Scale[6,7,31,34,37] and the phenotypic model.[29,35,36] Frailty varied from 20% to 82%, according to the scale and the population examined.
A direct comparison among some of these scales in hospitalized patients aged >65 years was reported by Pilotto et al., who described an innovative frailty instrument based on a modified CGA (CGA-based Multidimensional Prognostic Index -MPI).[38] The MPI integrated data from eight domains such as disability (Basic and instrumental activities of daily life–BADL- IADL), cognitive, nutritional, comorbidities, drug use, risk of developing pressure sores, and co-habitation status. ROC analysis for the endpoint of mortality showed good performance of MPI compared with FI and FI-CGA .

Value of Frailty instruments in measuring outcome

Frailty depends on several interrelated factors and can change over time. Since frailty is a dynamic process influenced by progressive aging,[39,40] it is uncertain whether it can be used as an outcome measure of an intervention.[41] Therefore, an evaluative outcome instrument to measure frailty with sound clinimetric properties is needed.[9] A review of many commonly adopted frailty instruments in clinical practice has analyzed their clinimetric properties (agreement, construct validity, responsiveness, interpretability, content validity, internal consistency, floor and ceiling effect).[42] Frailty instruments have mostly been validated as prognostic tools, but their ability for capturing intervention-induced changes in frailty over time is unclear. At the present time, and with caution, the FI calculated according to the deficit accumulation model[11,12] appears, from the clinimetric standpoint, the most suitable and reliable to capture changes in frailty over time. Using the frailty index as a tool to estimate the increase in healthcare resources required for different levels of frailty may help to identify the investment needed to reduce frailty in the community.[43,44]

Frailty in cardiology

With progressive population aging, the burden of cardiovascular disease has become prevalent as a cause of mortality, morbidity and disability.[45] Therefore, there has been a recent surge of interest in evaluating frailty in patients with cardiovascular conditions. Frailty has been assessed in patients affected by various cardiovascular diseases and many of the instruments adopted have demonstrated prognostic value;[46-48] they may have value in defining guidelines for cardiac patients' management during hospitalization and after discharge. Each of the instruments proposed has its own grade of complexity and prognostic information. In general, even as a sole prognostic indicator and with the above limitations, instruments describing a frailty status in several populations of cardiac patients have outscored other more usually adopted prognostic indicators .[46-48]

Frailty in elderly patients with acute coronary syndrome (ACS)PTCA

Many studies have evaluated frailty in elderly patients after an ACS or PTCA by using several instruments, such as the phenotypic model (PFI),[4] the CSHA Clinical Frailty Scale,[22] or the EFS.[23] In this setting frailty ranged from 10% to 48%, and higher levels of frailty were associated with worse outcomes (Table 5).[47, 49-54]

. These studies showed an independent added prognostic value of frailty assessment, and although larger studies are needed to refine risk prediction models, it is suggested that clinicians and researchers should consider how they can embed frailty measurement into clinical practice.

Frailty in elderly patients undergoing cardiac surgery

In the current era, the elderly represent the fastest growing group of patients referred for cardiac surgery, with the proportion of patients aged 75 years or older rising from 16% in 1990 to 25% in most recent estimates.[55] These complex and often frail patients are at increased risk of falls, prolonged hospitalization, mortality after surgery.[56,57] For this reason, many groups have evaluated preoperative frailty to increase prognostic capability.[55,58,59]

Recently, Afilalo et al.[55] in a population of 152 elderly patients (>70 years) undergoing coronary artery bypass graft and/or valve surgery, evaluated the incremental prognostic value of four different frailty scales and of three disability scales compared with classical cardiac surgery risk scores. Frailty Scales adopted in this study were the Fried frailty scale;[4] the expanded Fried frailty scale (addition of cognitive impairment and depressed mood);[60] the 4-item MacArthur Study of Successful Aging frailty scale sub-dimensions [gait speed, handgrip strength, inactivity, cognitive impairment];[61] and gait speed alone. Compared with the Parsonnet score[62] or the Society of Thoracic Surgeons Predicted Risk of Mortality or Major Morbidity score (STS-PROMM),[63] the addition of frailty and disability provided independent incremental value and improved model discrimination for in-hospital postoperative mortality or major morbidity. Thus, the integration of frailty, disability, and risk scores should better characterize elderly patients referred for cardiac surgery and identify those who are at increased risk.

Transvalvular aortic valve replacement (TAVR)

TAVR has shown to be a successful intervention in elderly patients with aortic stenosis, and patients after TAVR benefit from CR despite their older age and clinical complexity and frailty[64] . Several studies have recently described the added prognostic value of frailty evaluation over standard criteria in elderly patients undergoing TAVR

A modified Fried Frailty score (gait speed, grip strength, serum albumin, and activities of daily living) in very old patients was independently associated with increased 1-year mortality after TAVR. [65] A Frailty index based on assessment of cognition, mobility, nutrition, BADL and IADL predicted functional decline after TAVR, suggesting that this index might identify elderly patients who could potentially benefit from additional geriatric interventions. [66] Another study reported that a Multidimensional Geriatric Assessment (MGA)-based score (including cognition, nutrition, mobility, BADL, plus a 'home-made' frailty index) predicted 1 year mortality and major adverse cardiovascular and cerebral events (MACCE) after TAVR in patients aged >70 years.[67] Recently, a PARTNER Trial sub-study found that, in older recipients of TAVR, frailty, assessed using a modified frailty phenotype model (serum albumin, dominant handgrip strength, gait speed, and activity of daily living), independently predicted all-cause mortality or poor outcome at 1 year.[68]

A recent review of 6 studies and 4756 patients undergoing cardiac surgery or TAVR concluded that frail elderly patients have a higher likelihood of mortality, morbidity, functional decline, and MACCE following cardiac surgery or TAVR, regardless of the frailty assessment tool.[69]

All of the studies[65-69] have reported frailty measurement before surgery or intervention and utilized it as an added prognostic tool for later events, but none of these studies has evaluated frailty in the immediate post-operative period, which is usually unstable and therefore not well suited for measurements of frailty that require clinical stability.

Frailty in elderly patients with chronic heart failure /Left ventricular assist device

Frailty prevalence in chronic heart failure (CHF) patients ranges from 15% to 74%, depending on the population and assessment method . The FRAIL-HF study[70] reported that 70.2% of nondependent older patients hospitalized for CHF are frail as evaluated by the Fried criteria. In these patients a superimposition of primary frailty associated with progressive aging and frailty secondary to CHF is difficult to disentangle, since both share similar physiopathological mechanisms, such as anabolic–catabolic and neurohormonal imbalance, systemic inflammation, increased oxidative stress or mitochondrial dysfunction.[71] In CHF frailty is consistently associated with poor outcome, quality of life, disability or hospitalization.[72-80]

Mc Nallan et al. reported that frailty, measured by the Fried criteria, was an independent predictor of hospitalizations in community patients with CHF.[72] Cacciatore et al. utilizing the Lachs frailty staging score (based on sensorial compromise, cognitive impairment, urinary incontinence, poor social support and disability), found that the probability of death in patients with CHF and frailty score of 3 was 100% as compared with 55% in patients with CHF and frailty score of 1.[73] Lupon et al. found that a scale based on evaluation of BADL-IADL, cognitive function, psychologic and social status, was independently correlated with quality of life, hospitalization and mortality.[74,75]

Volpato et al.[76] and Chiarantini et al.[77] utilizing the Short Physical performance Battery (SPPB), a test measuring lower extremity physical performance by walking speed, balance test and ability to stand up from a chair,[78] found in patients hospitalized for CHF that poor SPPB scores at hospital discharge were predictive of a greater risk of rehospitalization or death. Even single items such as low gait speed or low grip strength in community living CHF patients were correlated with hospitalization at follow up,[79] and Barthel index of disability and cognitive compromise correlated with 6 months mortality in CHF patients admitted to hospital.[80]

Recently, Dunlay et al found, in a small cohort study of advanced CHF patients undergoing left ventricular assist device (LVAD) implantation, that pre-intervention frailty was associated with increased mortality.[81] This suggests that frailty assessment may be relevant for identifying suitable candidates for this invasive procedure. There is evidence that LVAD intervention[82] and heart transplantation[83] improve some biologic, structural, and functional markers of frailty associated with CHF.

Frailty and Cardiac Rehabilitation (CR)

Despite the negative bias for referring very elderly patients with complex comorbidities and frailty to CR,[84] at present patients older than 75 years represent about one third of those referred to CR.[85] Thus frailty might be present in a substantial proportion of patients admitted to CR, and this condition needs specific consideration.

The prevalence of frailty and its clinical and prognostic relevance has not as yet been well characterized in the environment of CR, although many studies have reported measurement of frailty in patients with coronary syndromes in ICU or in cardiology wards,[49-52] and others have underscored the close link between frailty and CHF.[71-80] Since patients after ACS or CHF represent a considerable proportion of those participating in CR,[85,86] we may suggest that frailty measurement should be performed in CR, to help plan their management and estimate their prognosis.

Frailty complicates the management of elderly patients, since it may affect the type and timing of diagnostic procedures and pharmacologic and non-pharmacologic treatment. Their baseline physical function evaluation should be tailored to their physical conditions, and the CR program should be individualized on the basis of their functional compromise and disability.[87] Pharmacologic treatment should be carefully weighted, balancing guidelines recommendations with a prudent approach, since associated comorbidities may increase iatrogenic complications. In community living or institutionalized frail elderly patients tailored exercise training has improved to some degree their physical function and quality of life.[88-93] Individuals at higher risk of disability at baseline derive the most benefit from these types of interventions[90] by increasing gait speed, improving balance, and performance in activities of daily life,[91] or SPPB.[92]. However, it is still uncertain whether these positive results can be applied to CR patients. Particularly in patients with CHF, structured exercise training improves the neurohormonal, inflammatory, and metabolic parameters of CHF-related frailty and has favorable effects on physical function, functional capacity and quality of life.[70] It is still uncertain whether therapeutic interventions (pharmacological and non-pharmacological) that have proven successful in younger CHF patients will be successful in elderly patients, since the majority of randomized clinical trials in CHF do not include very elderly patients with frailty. However, from a practical standpoint, exercise-based CR program should be implemented, with caution, aiming at obtaining improvement in physical mobility, functional capacity, fall prevention, disability prevention or decreased progression, and improvement in quality of life.

Nutrition is also a very important part of the multidimensional intervention in CR,[94] particularly in very elderly and frail or sarcopenic/cachectic patients, where a poor nutritional status is one of the main pathophysiologic mechanism for frailty. Recent studies suggest that improving nutritional status may reduce the risk of frailty.[95,96] Furthermore, a recent review has shown that nutrition may improve the functional outcome of elderly and frail patients.[97]

Future directions

Step 1: Feasibility of frailty measurement in the setting of cardiac rehabilitation

Assessment of frailty in the CR requires additional time within routine clinical evaluation. While the addition of frailty tools to the management of the elderly patient holds promise, multiple topics should be clarified before recommending their widespread clinical application. These include identifying which of the many tools provides the best combination of performance and facility, with clear definition of standardized values.

A variety of instruments for measuring frailty could be tested in CR and compared regarding their practical feasibility, trying to achieve a compromise between simplicity of administration and completeness of frailty domain representation. It is important to stress that the proposed tools should be selected among those already validated in hospitalized patients with cardiovascular disease, and particularly in patients after an acute coronary event or with CHF, who are likely to be similar to those admitted to CR programs. It is uncertain whether tools validated before the index event for CR or in other clinical setting may be applicable to patients after a cardiovascular acute event/intervention.

The EFS could be used as representative of a user friendly but comprehensive instrument (see also Table 3).[23] The EFS is easy to administer, requiring <5 min to be performed; it can be administered by any professional (nurse, technician) or student; and it has been validated in elderly patients after acute coronary syndromes,[49] where it was found to correlate with prognosis. It includes also 2 clinical performance items interrogating cognition (clock test) and functional performance

(Timed up and go-TUG-test). Despite that tools based on the deficit accumulation model, such as the 40 item FI adopted by Singh et al.[98] , adopted in elderly patients in acute geriatric rehabilitation wards, could be used to assess prognosis or guide intervention planning, or for evaluating frailty changes with time, in the busy Cardiac Rehabilitation word, tools based on deficit accumulation model may be cumbersome to be applied. Therefore, a more simple and handy tool based on a standardized subjective evaluation of frailty would be more easily accepted and adopted, such as the Canadian Study on Health and Ageing Clinical Frailty Scale[22] (Table 3)

These authors, through the EACPR, seek to evaluate the feasibility of applying these tools in CR centers through a European Registry study in all elderly patients over 75 years old. This would have the advantage of familiarizing the cardiologist working in CR with frailty instruments, whilst screening for the frequency of frail elderly patients enrolled in European cardiac rehabilitation centers.

Some practical points should be discussed, such as who carries out these measurements. It is the authors' opinion that, due to the simple nature of the data to be collected, any health professional (cardiologist, cardiologist in training, nurse, AHP or medical student) could perform a FI measurement, provided a uniform method of data collection is agreed and shared within and between CR centers

The timing of frailty assessment in CR is also relevant. It is the authors' opinion that frailty should be measured at admission to CR if the patient is already stable, or later as soon as clinical stability is reached in the course of the rehabilitative program. We believe that this approach is more correct, since before the acute event or surgery a frailty status may be worsened by the severity of disease, and may improve after clinical stabilization is reached in CR... On the other side, in patients entering CR after cardiac surgery, surgical complications in addition to a pre-surgical disability may limit their function, and it would be wise to wait for a progressive improvement in physical function before screening patients for frailty.

Step 2. Frailty and prognosis

It is still uncertain whether the addition of any frailty score/index to routine assessments in elderly patients entering CR may increase the prognostic capacity of that setting.

Therefore, these instruments should be tested in the CR environment as prognostic indicators against clearly defined end points, such as hospitalization length, functional capacity, quality of life, disability, and compared to traditional prognostic indicators. In this regard, a prospective observational study could be proposed for CR centers in Europe to evaluate the prognostic ability of frailty tools. If this is successful, CR practitioners may acquire an added tool to improve the prediction of outcomes, and be able to better tailor the type and intensity of interventions for frail patients.

In conclusion, it is the opinion of these authors that lead CR practitioners should work together with Geriatricians to become more familiar with frailty instruments and their application in the clinical environment in very elderly patients, to improve their prognostic ability and to design specific tailored interventions in complex patients. Further large studies can then be undertaken, to determine if the use of frailty measurement improves outcomes for elderly and frail patients admitted to CR.

Key messages

- Frailty is a condition specifically present in the elderly population, characterized by declining function of multiple physiologic systems associated with loss of physiologic reserves
- Two main models are proposed for frailty: phenotypic model (primary frailty) or deficits accumulation model (secondary frailty)
- Different instruments have been used to measure frailty
- Frailty correlates to medical outcomes in the elderly, independently of how it is measured
- Frailty has been shown to have prognostic value for patients with: coronary artery disease, cardiac surgery, TAVR, CHF and LVAD
- The prevalence, clinical and prognostic relevance of frailty in a CR environment has not yet been well characterized
- The presence and severity of frailty may modulate the CR program by and design tailored interventions
- We need to better understand to what extent CR may change the course and the prognosis of frailty, especially in cardiovascular patients, since exercise training and nutrition are well-known cornerstones in the management of elderly cardiac patients.

Recommended tools for frailty evaluation in CR		
Tool	Items	Reference
Edmonton frail scale	17 simple questions or tasks, assessing cognition, self-perceived health, dependence for ADL, social support, medication use, nutrition, mood, continence and functional performance. Each item is given from 0 to 2 points, and a frailty state is assigned to a global scores > 8/17	23
Clinical Frailty scale from the CSHA study	Frailty assessment tool in the domains of mobility, energy, physical activity, and function. Scale ranging from a level of 1 (very fit) to 8 (very severely frail)	22

Authorship

CV , AA, RB, UC, MC, CD, MCI, JPS, HV, SH, PD contributed to conception or design of work

CV, AA, MA ,PD contributed to acquisition, analysis, or interpretation for the work

CV, PD drafted the manuscript

CV, AA, MA, RB, UC, MC, CD, SH , MCI, JPS, HV, PD critically revised the manuscript

All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy

References

1. European Commission, Directorate-General for Research and Innovation. Population ageing in Europe: Facts, implications and policies. ISBN 978-92-79-35063-4. doi:10.2777/60452
2. Morley JE, Perry HM 3rd and Miller DK. Editorial. Something about frailty. *J Gerontol A Biol Sci Med Sci* 2002;57:M698-704
3. Rockwood K and Mitnitski A. Frailty defined by deficit accumulation and geriatric medicine defined by Frailty. *Clin Ger Med* 2011;27:17-26.

4. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001;56:M146-156.
5. Clegg A, Young J, Iliff S, et al. Frailty in elderly people. *Lancet* 2013;381:752-762.
6. Bagshaw SM, Stelfox HT, McDermid RC, et al. Association between frailty and short- and long-term outcomes among critically ill patients: a multicenter prospective cohort study. *CMAJ* 2014;186:E95-102.
7. Basic D and Shanley C. Frailty in an older inpatient population: using the clinical frailty scale to predict patient outcomes. *J Aging Health* 2015;27:670-685.
8. Fried LP, Ferrucci L, Darer J, Williamson JD and Anderson G. Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. *J Gerontol A Biol Sci Med Sci* 2004;59:255-263.
9. De Lepeleire J, Iliffe S, Mann E and Degryse JM. Frailty: an emerging concept for general practice. *Br J Gen Pract* 2009;59:e177-182.
10. Strindberg TE and Pitkala KH. Frailty in elderly people. *Lancet* 2007;21:369:1328-1329.
11. Rockwood K, Mitnitski A and Mac Knight C. Some mathematical models of frailty and their clinical implications. *Rev Clin Gerontol* 2002;12:109-117.
12. Rockwood K and Mitnitski. A Frailty in relation to the accumulation of deficits. *J Gerontol A Biol Sci Med Sci* 2007;62A:722-727.
13. Kulminski A, Yashin A, Arbeev K, et al. Cumulative index of health disorders as an indicator of aging-associated processes in the elderly: Results from analyses of the national long term care survey. *Mech Ageing Dev* 2007;128:250-258.
14. Searle SD, Mitnitski A, Gahbauer EA, et al. A standard procedure for creating a frailty index. *BMC Geriatrics* 2008;8:24.
15. Mitnitski A, Song X, Skoog I, et al. Relative fitness and frailty of elderly men and women in developed countries and their relationship with mortality. *J Am Geriatr Soc* 2005:53:2184-2189.
16. Romero-Ortuno R. The SHARE frailty instrument for primary care predicts mortality similarly to a frailty index based on comprehensive geriatric assessment. *Geriatr Gerontol Int* 2013;13:497-504.
17. Ensrud KE, Ewing SK, Cawthon PM, et al. A comparison of frailty indexes for the prediction of falls, disability, fractures, and mortality in older men. *J Am Geriatr Soc* 2009; 57:492-8.

18. Abellan van Kan G, Rolland YM, Morley JE and Vellas B. Frailty: towards a clinical definition. *J Am Dir Assoc* 2008;9:71-72.
19. Subra J, Gillette-Guyonnet S, Cesari M, et al. Platform Team. The integration of frailty into clinical practice: preliminary results from the Gérontopôle. *J Nutr Health Aging* 2012;16:714-720.
20. Schuurmans H, Steverink N, Lindenberg S, et al. Old or frail: what tells us more? *J Gerontol A Biol Sci Med Sci* 2004;59:M962-965.
21. Gobbens RJ, van Assen MA, Luijkx KG, et al. The Tilburg Frailty Indicator: psychometric properties. *J Am Med Dir Assoc* 2010;11:344-355
22. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. *CMAJ* 2005;173:489-495.
23. Rolfson DB, Majumdar SR, Tsuyuki RT, et al. Validity and reliability of the Edmonton Frail Scale. *Age Ageing* 2006;35:526-529.
24. Jones DM, Song X and Rockwood K. Operationalizing a frailty index from a standardized comprehensive geriatric assessment. *J Am Geriatr Soc* 2004;52:1929-1933.
25. Theou O, Thomas D. Brothers TD, Mitnitski A and Rockwood Kl. Operationalization of frailty using eight commonly used scales and comparison of their ability to predict all-cause mortality. *J Am Geriatr Soc* 2013;61:1537-1551.
26. Ellis G, Whitehead MA, O'Neill D, et al. Comprehensive geriatric assessment for older adults admitted to hospital. *Cochrane Database Syst Rev* 2011;7:CD006211.
27. Jones D, Song X, Mitnitski A and Rockwood K. Evaluation of a frailty index based on a comprehensive geriatric assessment in a population-based study of elderly Canadians. *Aging Clin Exp Res* 2005; 17:465-471.
28. Hubbard RE, Eeles EM, Rockwood MR, et al. Assessing balance and mobility to track illness and recovery in older inpatients. *J Gen Intern Med* 2011;26:1471-8.
29. Stiffler KA, Finley A, Midha S and Wilber ST. Frailty assessment in the emergency department. *J Emerg Med* 2013;45:291-298.
30. Evans SJ, Sayers M, Mitnitski A and Rockwood K. The risk of adverse outcomes in hospitalized older patients in relation to a frailty index based on a comprehensive geriatric assessment. *Age Ageing* 2014;43:127-132.

31. Kahlon S, Pederson J, Majumdaret SR, et al. Association between frailty and 30-day outcomes after discharge from hospital. *CMAJ* 2015;187:799-804.
32. Singh I., Gallacher J, Davis K, et al. Predictors of adverse outcomes on an acute geriatric rehabilitation ward. *Age Ageing* 2012;41:242-246.
33. Pilotto A , Rengo F, Marchionni N, et al. Comparing the prognostic accuracy for all-cause mortality of frailty instruments: a multicentre 1-year follow-up in hospitalized older patients. *PLoS One* 2012;7:e29090.
34. Wallis SJ, Wall J, Biram RW and Romero-Ortuno R. Association of the clinical frailty scale with hospital outcomes. *QJM* 2015;108:943-949.
35. Baldwin MR, Reid MC, Westlake AA, et al. The feasibility of measuring frailty to predict disability and mortality in older medical intensive care unit survivors. *J Crit Care* 2014;293:401-408.
36. Handforth C, Clegg A, Young C, et al. The prevalence and outcomes of frailty in older cancer patients: a systematic review. *Ann Oncol* 2015;26:1091-1101.
37. Alfaadel TA, Soroka SD, Kiberd BA, et al. Frailty and mortality in dialysis: evaluation of a clinical frailty scale*. Clin J Am Soc Nephrol* 2015;10:832-840.
38. Pilotto A, Ferrucci L, Franceschi M, et al. Development and validation of a multidimensional prognostic index for one year mortality from comprehensive geriatric assessment in hospitalized older patients. *Rejuvenation Res* 2008;11:151-161.
39. Peterson MJ, Giuliani C, Morey MC, et al. Physical activity as a preventative factor for frailty: the health, aging, and body composition study. *J Gerontol A Biol Sci Med Sci* 2009;64:61-68.
40. Chin A Paw MJ, van Uffelen JG, Riphagen I and van Mechelen W. The functional effects of physical exercise training in frail older people; a systematic review. *Sports Med* 2008;38,781-793.
41. Hubbard RE, Fallah N, Searle SD, Mitnitski A and Rockwood K. Impact of exercise in community-dwelling older adults. *PLoS One* 2009;4: e6174.
42. de Vries NM, Staal JB, van Ravensberg CD, et al. Outcome instruments to measure frailty: A systematic review. *Ageing Res Rev* 2011;10:104-114.
43. Comans TA, Peel NM, Hubbard RE, et al. The increase in healthcare costs associated with frailty in older people discharged to a post-acute transition care program. *Age Ageing* 2016;45:317-20.

44. Ekdahl AW, Alwin J, Eckerblad J, et al. Long-term evaluation of the ambulatory geriatric assessment: a frailty intervention trial (AGe-FIT): clinical outcomes and total costs after 36 months. *J Am Med Dir Assoc* 2016;17:263-8.
45. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics-2015 update: a report from the American Heart Association. *Circulation* 2015;131:e29-322.
46. Afilalo J, Alexander KP, Mack MJ, et al. Frailty assessment in the cardiovascular care of older adults. *J Am Coll Cardiol* 2014;63:747-62.
47. Sanchis J, Bonanad C, Ruiz V, et al. Frailty and other geriatric conditions for risk stratification of older patients with acute coronary syndrome. *Am Heart* J 2014;168:784-791.
48. Singh M, Stewart R and White H. Importance of frailty in patients with cardiovascular disease. *Eur Heart J* 2014;35:1726-1731.
49. Graham MM, Galbraith PD, O'Neill D, et al. Frailty and outcome in elderly patients with acute coronary syndrome. Can J Cardiol 2013;29:1610-1615.
50. Singh M, Rihal CS, Lennon RJ, et al. Influence of frailty and health status on outcomes in patients with coronary disease undergoing percutaneous revascularization. *Circ Cardiovasc Qual Outcomes* 2011;4:496-502.
51. Ekerstad N. Swahn E, Janzonet M, et al. Frailty is independently associated with 1-year mortality for elderly patients with non-ST-segment elevation myocardial infarction. *Eur J Prev Cardiol* 2014;21:1216-24 .
52. White HD, Westerhout CM, Alexander KP, et al; TRILOGY ACS investigators. Frailty is associated with worse outcomes in non-ST-segment elevation acute coronary syndromes: Insights from the TaRgeted platelet Inhibition to cLarify the Optimal strateGy to medicallY manage Acute Coronary Syndromes (TRILOGY ACS) trial. *Eur Heart J Acute Cardiovasc Care* 2016;5:231-242.
53. Sujino Y, Tanno J, Nakano S, et al. Impact of hypoalbuminemia, frailty, and body mass index on early prognosis in older patients (≥85 years) with ST-elevation myocardial infarction. *J Cardiol* 2015;66:263-268.
54. Murali-Krishnan R, Iqbal J, Rowe R, et al. Impact of frailty on outcomes after percutaneous coronary intervention: a prospective cohort study. *Open Heart* 2015;2:e000294.

55. Afilalo J, Mottillo S, Eisenberg MJ ,et al. Addition of Frailty and Disability to Cardiac Surgery Risk Scores Identifies Elderly Patients at High Risk of Mortality or Major Morbidity. Methods and Results. *Circ Cardiovasc Qual Outcomes* 2012;5:222-228.
56. Naughton C, Feneck RO and Roxburgh J. Early and late predictors of mortality following on-pump coronary artery bypass graft surgery in the elderly as compared to a younger population. *Eur J Cardiothorac Surg* 2009;36:621-627.
57. Lee DH, Buth KJ, Martin BJ, et al. Frail patients are at increased risk for mortality and prolonged institutional care after cardiac surgery. *Circulation* 2010;121:973-978.
58. Simon H, Sündermanna SH, Dademaschb A, et al. Frailty is a predictor of short- and mid-term mortality after elective cardiac surgery independently of age. *Interact Cardiovasc Thorac Surg* 2014;18:580-585.
59. Robinson TN, Eiseman B, Wallace JI, et al. Redefining geriatric preoperative assessment using frailty, disability and co-morbidity. *Ann Surg* 2009;250:449-455.
60. Rothman MD, Leo-Summers L and Gill TM. Prognostic significance of potential frailty criteria. *J Am Geriatr Soc* 2008;56:2211-2116.
61. Sarkisian CA, Gruenewald TL, John Boscardin W and Seeman TE. Preliminary evidence for subdimensions of geriatric frailty: the Macarthur study of successful aging. *J Am Geriatr Soc* 2008;56:2292-2297.
62. Bernstein AD and Parsonnet V. Bedside estimation of risk as an aid for decision-making in cardiac surgery. *Ann Thorac Surg* 2000;69:823-828.
63. Shahian DM, O'Brien SM, Filardo G, et al. The Society of Thoracic Surgeons 2008 cardiac surgery risk models, part 1: coronary artery bypass grafting surgery. *Ann Thorac Surg* 2009;88:S2-S22.
64. Völler H, Salzwedel A, Nitardy A, et al. Effect of cardiac rehabilitation on functional and emotional status in patients after transcatheter aortic-valve implantation. Eur J Prev Cardiol. 2015 May;22(5):568-74.
65. Green P, Woglom AE, Genereux P, et al. The impact of frailty status on survival after transcatheter aortic valve replacement in older adults with severe aortic stenosis: a single-center experience. *J Am Coll Cardiol Interv* 2012;5:974-81.

66. Schoenenbergern AW, Stortecky S, Neumann S, et al. Predictors of functional decline in elderly patients undergoing transcatheter aortic valve implantation (TAVI). *Eur Heart J* 2013;34:684-692.
67. Stortecky S, Schoenenberger AW, Moser A, et al. Evaluation of multidimensional geriatric assessment as a predictor of mortality and cardiovascular events after transcatheter aortic valve implantation. *J Am Coll Cardiol Interv* 2012;5:489-496.
68. Green P, Arnold SV, Cohen DJ, et al. Relation of frailty to outcomes after transcatheter aortic valve replacement (from the PARTNER Trial). Am J Cardiol 2015;116:264-269.
69. Sepehri A, Beggs T, Hassan A, et al. The impact of frailty on outcomes after cardiac surgery: a systematic review. *J Thorac Cardiovasc Surg* 2014;148:3110-3117.
70. Vidan MT, Sanchez E, Fernandez-Aviles F, et al. FRAIL-HF, a study to evaluate the clinical complexity of heart failure in nondependent older patients: rationale, methods and baseline characteristics. *Clin Cardiol* 2014;37:725-732.
71. Goldwater DS and Pinney SP. Frailty in advanced heart failure: a consequence of aging or a separate entity? Clin Med Insights Cardiol 2015;9(suppl 2):39-46.
72. McNallan SM, Singh M, Chamberlain AM, Kane RL, et al. Frailty and healthcare utilization among patients with heart failure in the community. JACC Heart Fail 2013;1:135-141.
73. Cacciatore F, Abete P, Mazzella F, et al. Frailty predicts long-term mortality in elderly subjects with chronic heart failure. *Eur J Clin Invest* 2005;35:723-730.
74. McNallan SM, Chamberlain AM, Gerber Y, et al. Measuring frailty in heart failure: a community perspective. *Am Heart J* 2013;166:768-774.
75. Lupón J, González B, Santaeugenia S, et al. Prognostic implication of frailty and depressive symptoms in in an outpatient population with heart failure. *Rev Esp Cardiol* 2008;61:835-842.
76. Volpato S, Cavalieri M, Sioulis F et al. Predictive value of the short physical performance battery following hospitalization in older patients. *J Gerontol A Biol Sci Med Sci* 2011;66A:89-96.
77. Chiarantini D, Volpato S, Sioulis F, et al. Lower extremity performance measures predict long-term prognosis in older patients hospitalized for heart failure. *J Card Fail* 2010;16:390-395.
78. Guralnik JM, Simonsick EM, Ferrucci L, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. *J Gerontol* 1994;49:M85-94.

79. Chaudhry SI, McAvay G, Chen S, et al. Risk factors for hospital admission among older persons with newly diagnosed heart failure: findings from the Cardiovascular Health Study. *J Am Coll Cardiol* 2013;61:635-642.
80. Rozzini R, Sabatini T, Frisoni GB and Trabucchi M. Frailty is a strong modulator of heart failure-associated mortality. *Arch Intern Med* 2003;163:737-738.
81. Dunlay SM, Park SJ, Joyce LD, et al. Frailty and outcomes following implantation of Left ventricular assist device as destination therapy. *J Heart Lung Transplant* 2014;33: 359-365.
82. Khawaja T, Chokshi A, Ji R, et al. Ventricular assist device implantation improves skeletal muscle function, oxidative capacity, and growth hormone/insulin-like growth factor-1 axis signaling in patients with advanced heart failure. *J Cachexia Sarcopenia Muscle* 2014;5:297-305.
83. Habedank D, Ewert R, Hummel M, et al. Changes in exercise capacity, ventilation, and body and body weight following heart transplantation. *Eur J Heart Fail* 2007;9:310-316.
84. Brown TM, Hernandez AF, Bittner V, et al; American Heart Association Get With The Guidelines Investigators. Predictors of cardiac rehabilitation referral in coronary artery disease patients: findings from the American Heart Association's Get With The Guidelines Program. *J Am Coll Cardiol* 2009 Aug 4;54:515-521.
85. Giallauria F, Vigorito C, Tramarin R, et al; ISYDE-2008 Investigators of the Italian Association for Cardiovascular Prevention, Rehabilitation and Prevention. Cardiac rehabilitation in very old patients: data from the Italian Survey on Cardiac Rehabilitation-2008 (ISYDE-2008)--official report of the Italian Association for Cardiovascular Prevention, Rehabilitation, and Epidemiology. *J Gerontol A Biol Sci Med Sci* 2010;65:1353-1361.
86. Giallauria F, Fattirolli F, Tramarin R, et al; ISYDE-2008 Investigators of the Italian Association for Cardiovascular Prevention and Rehabilitation (GICR-IACPR). Cardiac rehabilitation in chronic heart failure: data from the Italian SurveY on carDiac rEhabilitation (ISYDE-2008). *J Cardiovasc Med (Hagerstown)* 2014;15:155-163.
87. Vigorito C, Incalzi RA, Acanfora D, et al; Gruppo Italiano di Cardiologia Riabilitativa e Preventiva. Recommendations for cardiovascular rehabilitation in the very elderly. *Monaldi Arch Chest Dis* 2003;60:25-39.

88. Faber MJ, Bosscher RJ, Chin A, Paw MJ and van Wieringen PC. Effects of exercise programs on falls and mobility in frail and pre-frail older adults: a multicenter randomized controlled trial. *Arch Phys Med Rehabil* 2006;87:885-896.
89. Binder EF, Schechtman KB, Ehsani AA, et al. Effects of exercise training on frailty in community-dwelling older adults: results of a randomized, controlled trial. *J Am Geriatr Soc* 2002;50:1921-1928.
90. Cesari M, Vellas B, Hsu FC, et al; LIFE Study Group. A physical activity intervention to treat the frailty syndrome in older persons-results from the LIFE-P study. *Gerontol A Biol Sci Med Sci* 2015;70:216-222.
91. Chou CH, Hwang CL and Wu YT. Effect of exercise on physical function, daily living activities, and quality of life in the frail older adults: a meta-analysis. *Arch Phys Med Rehabil* 2012;93:237-44.
92. Giné-Garriga M, Roqué-Fíguls M, Coll-Planas L, et al. Physical exercise interventions for improving performance-based measures of physical function in community-dwelling, frail older adults: a systematic review and meta-analysis. *Arch Phys Med Rehabil* 2014;95:753-769.
93. Weening-Dijksterhuis E, de Greef MH, Scherder EJ, et al. Frail institutionalized older persons: a comprehensive review on physical exercise, physical fitness, activities of daily living, and quality-of-life. *Am J Phys Med Rehabil* 2011;90:156-168.
94. Balady GJ1, Williams MA, Ades PA, et al. Core components of cardiac rehabilitation/secondary prevention programs: 2007 update: a scientific statement from the American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee, the Council on Clinical Cardiology; the Councils on Cardiovascular Nursing, Epidemiology and Prevention, and Nutrition, Physical Activity, and Metabolism; and the American Association of Cardiovascular and Pulmonary Rehabilitation. *Circulation* 2007;115:2675-2682.
95. Bonnefoy M, Berrut G, Lesourd B, et al. Frailty and nutrition: searching for evidence. *J Nutr Health Aging* 2015;19:250-257.
96. Smit E, Winters-Stone KM, Loprinzi PD, et al. Lower nutritional status and higher food insufficiency in frail older US adults. Br J Nutr 2013;110:172-178.
97. Bibas L, Levi M, Bendayan M, et al. Therapeutic interventions for frail elderly patients: part I. Published randomized trials. *Prog Cardiovasc Dis* 2014;57:134-143.

98. Singh I, Gallacher J and Davis K. Predictors of adverse outcomes on an acute geriatric rehabilitation ward. *Age Ageing* 2012;41:242-246.
99. Hamilton BB, Granger CV, Shervin FS, et al. A uniform national data system for medical rehabilitation. In: Further MJ, ed. Rehabilitation outcomes: analysis and measurements. Baltimore: Paul H Brooks, 1987.